REMARKS

Claims 10-21, 23-30, 37-42, 45 and 53-66 are pending in the present application. Claims 10, 53, 59, 62 and 64 are amended and claims 13 and 63 are cancelled without prejudice or disclaimer of the subject matter contained therein. Claims 65 and 66 are newly added. Claims 10, 23, 59, 62 and 65-66 are the independent claims.

Applicants respectfully note that the present action indicates that the drawings have been accepted by the Examiner. Office Action, Summary at 10.

Applicants also respectfully note that the present action does not indicate that the claim to foreign priority under 35 U.S.C. §119 has been acknowledged or that certified copies of all priority documents have been received by the U.S.P.T.O. Applicants respectfully request that the Examiner's next communication include an indication as to the claim to foreign priority under 35 U.S.C. §119 and an acknowledgement of receipt of the certified copies of all priority documents.

Claim Objections

Claims 53 and 64 are objected to because of certain informalities. Applicants have amended claims 53 and 64 to correct minor typographical errors. Therefore, withdrawal of the objection to claims 53 and 64 is respectfully requested.

Example Embodiments of the Present Application

Independent claims 10, 23, 59, 62 and 65-66 recite the use of a fluid bed dry granulation method. Non-limiting example embodiments of this feature can be found, for example, in paragraph [0031]. In accordance with the fluid bed dry granulation method, the primary particles are dried while spraying liquid containing a binder to the primary particles in a fluid state, so as to secondarily clump the primary particles

via the binder. Therefore, it is possible not only to produce the drug containing composite particles with efficiency and quality but also to control a condition under which the nano particles are clumped. As a result, it is possible to further improve the handling property of the drug containing composite particles without losing advantages of the nano particle.

Claim Rejections – 35 U.S.C. § 103

Trofast/Dickinson

Claims 10-11, 13-15 and 38-39 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Trofast *et al.* (WO 95/09616, hereinafter "Trofast") in view of Dickinson *et al.* (WO 01/78689, hereinafter "Dickinson"). Applicants respectfully traverse this rejection for the reasons detailed below.

In the Office Action, the Examiner states that a systematic agitation method is the same as a fluid bed dry granulation method. Applicants respectfully disagree. As described above, the fluid bed dry granulation method and the use of a binder in clumping the primary particles is completely different from a systematic agitation method as described in Trofast. Applicants respectfully submit that page 2, lines 10-15 of Trofast teach away from the fluid bed dry granulation method because the powder can be granulated or pelletized **without a binder** by systematic agitation of the particulate material. Dickinson does not disclose a granulation method. Therefore, neither Trofast, Dickinson nor the combination thereof teaches or suggests "a combining step of combining the primary particles with each other so that the primary particles are reversibly collected, wherein a drug powder is used as the nano particles and the primary particles are subjected to secondary granulation in a fluid bed dry granulation method" as recited in amended independent claim 10.

Claims 11, 13-15 and 38-39, dependent on independent claim 10, are patentable for the reasons stated above with respect to claim 10 as well as for their own merits.

The Applicants, therefore, respectfully request that the rejection to Claims 10-11, 13-15 and 38-39 under 35 U.S.C. § 103(a) be withdrawn.

Trofast/Kawashima/Dickinson

Claims 10-12 and 37 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Trofast in view of Kawashima (Advanced Drug Delivery Reviews 2001 47:1-2, hereinafter "Kawashima") and as evidenced by Dickinson. Applicants respectfully traverse this rejection for the reasons detailed below.

As described above, the fluid bed dry granulation method and the use of a binder in clumping the primary particles is completely different from a systematic agitation method as described in Trofast. Applicants respectfully submit that page 2, lines 10-15 of Trofast teach away from the fluid bed dry granulation method because the powder can be granulated or pelletized **without a binder** by systematic agitation of the particulate material. Dickinson and Kawashima do not disclose a granulation method. Therefore, neither Trofast, Kawashima, Dickinson nor the combination thereof teaches or suggests "a combining step of combining the primary particles with each other so that the primary particles are reversibly collected, wherein a drug powder is used as the nano particles and the primary particles are subjected to secondary granulation in a fluid bed dry granulation method" as recited in amended independent claim 10.

Claims 11-12 and 37, dependent on independent claim 10, are patentable for the reasons stated above with respect to claim 10 as well as for their own merits.

The Applicants, therefore, respectfully request that the rejection to Claims 10-12 and 37 under 35 U.S.C. § 103(a) be withdrawn.

Trofast/Dickinson/Nakagami

Claims 10 and 15-16 are rejected under 35 U.S.C. §103(a) as being unpatentable over Trofast in view of Dickinson as applied to claims 10-11, 13-15 and 38-39 above, and further in view of Nakagami *et al.* (U.S. Patent No. 6,335,036, hereinafter "Nakagami"). Applicants respectfully traverse this rejection for the reasons detailed below.

As described above, the fluid bed dry granulation method and the use of a binder in clumping the primary particles is completely different from a systematic agitation method as described in Trofast. Applicants respectfully submit that page 2, lines 10-15 of Trofast teach away from the fluid bed dry granulation method because the powder can be granulated or pelletized **without a binder** by systematic agitation of the particulate material. Dickinson and Nakagami do not disclose a granulation method. Therefore, neither Trofast, Dickinson, Nakagami nor the combination thereof teaches or suggests "a combining step of combining the primary particles with each other so that the primary particles are reversibly collected, wherein a drug powder is used as the nano particles and the primary particles are subjected to secondary granulation in a fluid bed dry granulation method" as recited in amended independent claim 10.

Claims 15-16, dependent on independent claim 10, are patentable for the reasons stated above with respect to claim 10 as well as for their own merits.

The Applicants, therefore, respectfully request that the rejection to Claims 10 and 15-16 under 35 U.S.C. § 103(a) be withdrawn.

Ishizaka/Trofast/Jain '506

Claims 10-11, 17-19, 40-41, 59-61 and 63-64 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ishizaka *et al.* (U.S. Patent No. 5,336,271, hereinafter "Ishizaka") in view of Trofast and Jain *et al.* (U.S. Patent No. 6,165,506, hereinafter "Jain '506"). Applicants respectfully traverse this rejection for the reasons detailed below.

As described above, the fluid bed dry granulation method and the use of a binder in clumping the primary particles is completely different from a systematic agitation method as described in Trofast. Applicants respectfully submit that page 2, lines 10-15 of Trofast teach away from the fluid bed dry granulation method because the powder can be granulated or pelletized **without a binder** by systematic agitation of the particulate material. Ishizaka and Jain do not disclose a granulation method. Therefore, neither Ishizaka, Trofast, Jain nor the combination thereof teaches or suggests "a combining step of combining the primary particles with each other so that the primary particles are reversibly collected, wherein a drug powder is used as the nano particles and the primary particles are subjected to secondary granulation in a fluid bed dry granulation method" as recited in amended independent claim 10 or "a combining step of combining a first primary particle and a second primary particle with each other so that the first and second primary particles are reversibly collected, so as to form a polymer nano composite particle, wherein the first and second primary particles are combined with each other using a fluid bed dry granulation method" as recited in amended independent claim 59.

Claims 11, 17-19, 40-41, 60-61 and 63-64, dependent on independent claims 10 and 59, are patentable for the reasons stated above with respect to claims 10 and 59 as well as for their own merits.

The Applicants, therefore, respectfully request that the rejection to Claims 10-11, 17-19, 40-41, 59-61 and 63-64 under 35 U.S.C. § 103(a) be withdrawn.

Ishizaka/Trofast/Jain '506/Bruno

Claims 10, 17, 18, 20-21, 42, 59 and 62 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ishizaka in view of Trofast and Jain '506 as applied to claims 10, 17-19, 40-41, 59-61 and 63-64 above, and further in view of Bruno *et al.* (U.S. Patent No. 5,518,187, hereinafter "Bruno"). Applicants respectfully traverse this rejection for the reasons detailed below.

As described above, the fluid bed dry granulation method and the use of a binder in clumping the primary particles is completely different from a systematic agitation method as described in Trofast. Applicants respectfully submit that page 2, lines 10-15 of Trofast teach away from the fluid bed dry granulation method because the powder can be granulated or pelletized **without a binder** by systematic agitation of the particulate material. Ishizaka and Jain do not disclose a granulation method and Bruno teaches modifying the surface of the drug powder by milling. Therefore, neither Ishizaka, Trofast, Jain, Bruno nor the combination thereof teaches or suggests "a combining step of combining the primary particles with each other so that the primary particles are reversibly collected, wherein a drug powder is used as the nano particles and the primary particles are subjected to secondary granulation in a fluid bed dry granulation method" as recited in amended independent claim 10, "a combining step of combining a first primary particle and a second primary particle with each other so that the first and second primary particles are reversibly collected, so as to form a polymer nano composite particle, wherein the first and second primary particles are combined with each other using a fluid bed dry granulation method" as recited in amended independent claim 59 or "a carrier particle surface modification step of

modifying the surface of the carrier particle, using the fluid bed dry granulation method or the dry mechanical particle combining method, before carrying out the combining step" as recited in newly added independent claims 65-66.

Furthermore, with regards to claim 62, on pages 8-9 of the Office Action, the Examiner states that Bruno teaches using other particles that are often used as lubricants (e.g. copolymers of lactide and glycolide) to mill (modify the surface) the particles used in pharmaceutical preparations. The Examiner also states that it would have been obvious to one of ordinary skill in the art to use the milling method of Bruno on the polymer particles to improve the dissolution properties of the composite particle made by the method of Ishizaka modified by Trofast and Jain. At page 18, line 14 of the Office Action, the Examiner also states that Bruno discloses a dry grinding process. However, the career particle 63 is combined to a polymer as a lubricant **before** the obtained particle is combined to a nano particle clump of a drug as illustrated on pages 60-61 of the Specification as filed. Therefore, neither Ishizaka, Trofast, Jain, Bruno nor the combination thereof teaches or suggests "a carrier surface modification step of modifying a surface of a carrier particle by combining the carrier particle and the biocompatible polymer, wherein the biocompatible polymer is a lubricant ... and in the combining step, the primary particles are made to adhere to a surface of each of the modified carrier particles" as recited in amended independent claim 62.

Claims 17, 18, 20-21, and 42, dependent on independent claims 10, 59 and 62, are patentable for the reasons stated above with respect to claims 10, 59 and 62s well as for their own merits.

The Applicants, therefore, respectfully request that the rejection to Claims 10, 17, 18, 20-21, 42, 59 and 62 under 35 U.S.C. § 103(a) be withdrawn.

Ishizaka/Trofast/Jain'506/Hosokawa

Claims 10 and 53-55 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ishizaka in view of Trofast and Jain '506 as applied to claims 10, 17-19, 40-41, 59-61 and 63-64 above, and further in view of Hosokawa *et al.* (U.S. Patent No. 4,789,105, hereinafter "Hosokawa"). Applicants respectfully traverse this rejection for the reasons detailed below.

As described above, the fluid bed dry granulation method and the use of a binder in clumping the primary particles is completely different from a systematic agitation method as described in Trofast. Applicants respectfully submit that page 2, lines 10-15 of Trofast teach away from the fluid bed dry granulation method because the powder can be granulated or pelletized **without a binder** by systematic agitation of the particulate material. Ishizaka, Jain and Hosokawa do not disclose a granulation method. Therefore, neither Ishizaka, Trofast, Jain, Hosokawa nor the combination thereof teaches or suggests "a combining step of combining the primary particles with each other so that the primary particles are reversibly collected, wherein a drug powder is used as the nano particles and the primary particles are subjected to secondary granulation in a fluid bed dry granulation method" as recited in amended independent claim 10.

Claims 53-55, dependent on independent claim 10, are patentable for the reasons stated above with respect to claim 10 as well as for their own merits.

The Applicants, therefore, respectfully request that the rejection to Claims 10 and 53-55 under 35 U.S.C. § 103(a) be withdrawn.

Ishizaka/Jain '029/Ryde

Claims 23-27, 30 and 45 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ishizaka in view of Jain *et al.* (U.S. Patent No. 6,316,029,

hereinafter "Jain '029") and Ryde *et al.* (U.S. Patent No. 6,375,986, hereinafter "Ryde"). Applicants respectfully traverse this rejection for the reasons detailed below.

Applicants respectfully submit that none of the cited art teaches or suggests "making a mixture, containing nano particles... and a drug powder ... into a composite particle using a fluid bed dry granulation method or a dry mechanical particle combining method, so as to modify a surface of the drug powder" as recited in claim 23. Ishizaka and Jain make no mention of modifying the surface of the drug powder, and Ryde teaches modifying the surface of a drug powder with the use of a surface stabilizer, rather than a fluid bed dry granulation method or a dry mechanical particle combining method as recited in independent claim 23.

Claims 24-27, 30 and 45, dependent on independent claim 23, are patentable for the reasons stated above with respect to claim 23 as well as for their own merits.

The Applicants, therefore, respectfully request that the rejection to Claims 23-27, 30 and 45 under 35 U.S.C. § 103(a) be withdrawn.

Ishizaka/Jain '506/Ryde/Kawashima/Murakami

Claims 23-24 and 28-29 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ishizaka in view of Jain '506 and Ryde as applied to claims 23-27, 30 and 45 above, and further in view of Kawashima and Murakami *et al.* (Advanced Powder Technology 2000 11:311-322, hereinafter "Murakami"). Applicants respectfully traverse this rejection for the reasons detailed below.

As stated above, Applicants respectfully submit that none of the cited art teaches or suggests "making a mixture, containing nano particles... and a drug powder ... into a composite particle using a fluid bed dry granulation method or a dry mechanical particle combining method, so as to modify a surface of the drug powder" as recited in claim 23. Ishizaka, Jain, Kawashima and Murakami make no mention of

modifying the surface of the drug powder, and Ryde teaches modifying the surface of a drug powder with the use of a surface stabilizer, rather than a fluid bed dry granulation method or a dry mechanical particle combining method as recited in independent claim 23.

Claims 24 and 28-29, dependent on independent claim 23, are patentable for the reasons stated above with respect to claim 23 as well as for their own merits.

The Applicants, therefore, respectfully request that the rejection to Claims 23-24 and 28-29 under 35 U.S.C. § 103(a) be withdrawn.

Ishizaka/Jain '506/ Ryde/Hosokawa

Claims 23 and 56-58 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ishizaka in view of Jain '506 and Ryde as applied to claims 23-27, 30, and 45 above, and further in view of Hosokawa. Applicants respectfully traverse this rejection for the reasons detailed below.

As stated above, Applicants respectfully submit that none of the cited art teaches or suggests "making a mixture, containing nano particles... and a drug powder ... into a composite particle using a fluid bed dry granulation method or a dry mechanical particle combining method, so as to modify a surface of the drug powder" as recited in claim 23. Ishizaka, Jain and Hosokawa make no mention of modifying the surface of the drug powder, and Ryde teaches modifying the surface of a drug powder with the use of a surface stabilizer, rather than a fluid bed dry granulation method or a dry mechanical particle combining method as recited in independent claim 23.

Claims 56-58, dependent on independent claim 23, are patentable for the reasons stated above with respect to claim 23 as well as for their own merits.

The Applicants, therefore, respectfully request that the rejection to Claims 23 and 56-58 under 35 U.S.C. § 103(a) be withdrawn.

Double Patenting Rejections

A. Claims 10 and 23-24 are rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 12 and 16 of U.S. Patent No. 7,022,311.

Applicants refer to the arguments above regarding claims 10 and 23 and respectfully submit that claims 12 and 16 of the '311 patent do not teach or suggest "a combining step of combining the primary particles with each other so that the primary particles are reversibly collected, wherein a drug powder is used as the nano particles and the primary particles are subjected to secondary granulation in a fluid bed dry granulation method" as recited in independent claim 10 or "making a mixture, containing nano particles... and a drug powder ... into a composite particle using a fluid bed dry granulation method or a dry mechanical particle combining method" as recited in independent claim 23.

B. Claims 10 and 23-24 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 22 and 31-34 of co-pending U.S. Application No. 12/068,499 (12480-000063/US/DVA).

Applicants respectfully submit that the double patenting rejection in view of co-pending U.S. Application No. 12/068,499 is incorrect. MPEP 804 states "a double patenting rejection is not permitted where the claimed subject matter is presented in a divisional application as a result of a restriction requirement made in a parent application".

Therefore, withdrawal of the obviousness-type double patenting rejections of claims 10 and 23-24 is respectfully requested.

CONCLUSION

Accordingly, in view of the above amendments and remarks, reconsideration of the objections and rejections and allowance of each of claims 10-20, 23-30, 37-42, 45, 53-64 in connection with the present application is earnestly solicited.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 08-0750 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. §1.17; particularly, extension of time fees.

Respectfully submitted,

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